GEORGETOWN UNIVERSITY MEDICAL CENTER

Department of Pharmacology

July 1, 1999

Dockets Management Branch (HFA- 305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

RE: Docket #99N-0188

Gentlemen:

I am writing in response to the item cited above regarding proposed labeling changes for progestational agents for human use.

Presently the FDA requires patient labeling and professional labeling for progestational drug products which warn against the increased risk of birth defects associated with these products during the first 4 months of pregnancy. It is this requirement which the FDA proposed to revoke. As stated in the Federal Register release on page 1:

> FDA has concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted. In addition, the diversity of drugs which can be described as **progestational**, and the diversity of conditions that these drugs may be used to treat, make it inappropriate to consider these drugs a single class for labeling purposes. This action is intended to provide consumers with more appropriate labeling for certain drug products.

The concern I wish to raise with the FDA's proposed action is that it suffers from the same logical defect as the problem it is designed to solve. Once implemented, all teratogenic warnings will be removed from all progestational drug product labeling. Whereas now the problem is that there are teratogenic warnings for products where there may be no scientific evidence to support them, e.g., progesterone, after the proposed rule change there will be, in my view, a worse problem. That problem will be that known teratogens within the class, such as norethindrone, will have no teratogenic warnings.

3900 Reservoir Road NW Washington DC 20007-2195 USA
202-687-1057 FAX: 202-687-6437

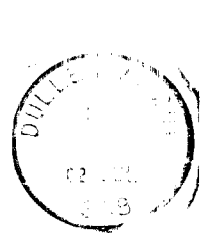
Please allow me to suggest that a logical and scientifically valid approach would be to have labeling of each progestational drug product accurately reflect the state (or lack) of knowledge about teratogenic potential for each individual agent. I see no reason to assume that if progesterone is not a human teratogen, that all members of the progestin class are safe in pregnancy, and there is credible evidence to the contrary. If the ACOG is having difficulty with teratogenic warnings for progesterone because patients are being unjustifiably alarmed, then the remediation should be limited to progesterone. Similarly, labeling of estrogen-MPA products intended for post-menopausal women need not address pregnancy warnings, as they do not apply to this class of patients. To remove warnings from all members of this class, however, represents a step backwards from FDA's consumer protection mandate and virtually guarantees that FDA will have to re-visit this issue at some time in the near future, as the role of these agents as human teratogens continues to be argued in the literature. A credible policy would require each individual progestational drug product to carry warnings appropriate to that particular product.

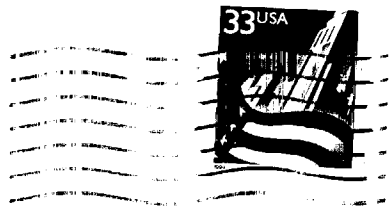
Possibly this is FDA's intention. If so, however, it is not clear from the Federal Register notice. The proposed rule speaks to eliminating teratogenic warnings from all drugs within the class. It does not speak to any process for retaining teratogenic warnings for particular progestational drug products for which they are appropriate.

Sincerely yours,

Arthur Raines, Ph.D.
Professor Emeritus of Pharmacology/Neurology

A. Raines, Ph.D.
GEORGETOWN UNIVERSITY MEDICAL CENTER
Department of Pharmacology
3900 Reservoir Road NW Washington DC 20007-2195 USA





Dockets Management Branch (HFA- 305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

RE: Docket #99N-0188

20857+0001